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L4: Entry 16 of 17 File: USPT May 22, 2001

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DOCUMENT-IDENTIFIER: US 6235481 B1
TITLE: Polynucleotides encoding calpain 10

Drawing Description Text (11):
FIG. 9A, FIG. 9B and FIG. 9C. Effect of protease inhibitors on the insulin secretory response to glucose and other secretagogues in mouse pancreatic islets. FIG. 9A Insulin secretion by islets incubated at various glucose concentrations in the absence (open bars) and presence (hatched bars) of 100 .mu.M ALLM. Results are mean .+-.SEM of 4-7 studies per group. *p<0.05 compared to islets incubated in the absence of ALLM. FIG. 9B. Insulin secretion by perifused islets in response to stimulation with 20 mM glucose (6-20min, solid bar). The perifusate contained 2 mM glucose except where shown. Islets were preincubated for 4 hr either in the absence of calpain inhibitors (.box-solid.) or in the presence of 100 .mu.M ALLM (.circle-solid.) or 200 .mu.M E-64-d (.tangle-solidup.). In studies involving inhibitors, ALLM was present throughout the study but E-64-d which is an irreversible cysteine protease inhibitor was present only during the pre-incubation. Results are mean .+-.SEM of 3 studies in each group. FIG. 9C. Insulin secretion by mouse islets incubated in the presence of 2 mM glucose (2), 8 mM glucose (8), 250 .mu.M carbachol (CCh) or 50 nM GLP-1 (GLP-1) in the presence of 8 mM glucose and 30 mM KCl in the presence of 2 mM glucose (KCl). Islets were incubated either in the absence (open bars) or presence (hatched bars) of 100 .mu.M ALLM. Results are mean .+-.SEM of 6 separate studies. *p<0.05 compared to islets incubated in the absence of ALLM.

Detailed Description Text (25):
Some patients are virtually impossible to treat with insulin because their cells cannot effectively utilize or are resistant to insulin therapy. As a result of the lack of glycemic control, diabetic patients often experience a variety of conditions including: neuropathy, nephropathy, cardiomyopathy, fetinopathy, coronary and peripherovascular disease and the like. These complications occur due to the unachieved glycemic control that results from failure of the insulin, diet and/or exercise only approach.

Detailed Description Text (473):
Animals. Studies were performed on islets obtained from non-fasted 9-13 wk old C57BL/6J mice (Jackson, Bar Harbor, Me.) and adipocytes and soleus muscles isolated from 8-12 wk old normal Wistar rats (Harlan Sprague-Dawley, Indianapolis, Ind.). The calpain inhibitors used were ALLM (N-Ac-Leu-Leu-methioninal, Calbiochem-Novabiochem, Inc, San Diego, Calif.) and E-64-d (ethyl (+)-(2S,3S)-3-[(S)-3-Methyl-1-(3-methylbutylcarbamoyl)butyl-carbamoyl]-2-oxiranecarboxylate, Matreya Inc., Pleasant Gap, Pa.). The calpain inhibitors were dissolved in DMSO. GLP-1 (7-36 amide) was from Peninsula Laboratory (Belmont, Calif.).

Detailed Description Text (490):
ALLM (250 .mu.M) and E-64-d (200 .mu.M) increased the insulin secretory responses to 20 mM glucose in isolated pancreatic islets by 1.97.+-.0.3-fold (n=5, p<0.01, (mean.+-.SEM)) and 1.77.+-.0.1-fold (n=6, p<0.001), respectively (FIG. 8A and FIG. 8B). These effects were not observed at 2 mM glucose. The effects of ALLM and E-64-d on the insulin secretory response to 20 mM glucose (FIG. 8C and FIG. 8D) were seen at inhibitor concentrations greater than 100 .mu.M and were glucose dependent in that the insulin secretory response was enhanced at glucose concentrations above 8 mM glucose but significant effects were not observed at 2,4 or 6 mM glucose (FIG. 9A). The

enhancement of the insulin secretory response to 20 mM glucose by ALLM and E-64-d was also observed in a dynamic islet perifusion system (FIG. 9B). ALLM produced a small but statistically significant increase in the insulin secretory response to 50 nM GLP-1 (1.55.+-.0.2-fold, n=6, p<0.05), an agent which stimulates adenyl cyclase. ALLM did not however significantly increase the insulin secretory responses to 30 mM KCl, an agent which directly depolarizes the .beta.-cell (FIG. 9C) or 100 .mu.M carbachol (CCh) which mobilizes Ca.sup.2+ from intracellular stores.

Detailed Description Text (500):
The present studies also provide insight into the molecular mechanism by which ALLM and E-64-d increase the insulin secretory responses to glucose and GLP-1. These agents did not lead to an increase in [Ca.sup.2+].sub.i, rates of glucose oxidation and utilization, or NAD(P)H generation. Thus, they do not affect pathways in the .beta.-cell responsible for the uptake and metabolism of glucose. Rather, the inventors believe that the most likely site(s) of action are in pathways that regulate the movement or fusion of insulin secretory granules with the plasma membrane.

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L4: Entry 14 of 17 File: USPT Jun 4, 2002

DOCUMENT-IDENTIFIER: US 6399601 B1
TITLE: Bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors

Brief Summary Text (156):
GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2 ;

Brief Summary Text (175):
In another preferred embodiment of the kits, the second compound is selected from LysPro insulin, GLP-1 (7-37) (insulinotropin), GLP-1 (7-36)-NH.sub.2, chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; metformin, phenformin, buformin, midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan, linogliride, ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone, clomoxir, etomoxir. acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945, BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, L-386,398; benfluorex, fenfluramine, Naglivan.RTM., (bis(cysteinamide N-octyl)oxovanadium) acpimox, WAG 994, Symlin.TM., (pramlintide acetate)-AC2993 and nateglinide.

Brief Summary Text (265):
Representative agents that can be used to treat diabetes include insulin and insulin analogs: (e.g., LysPro insulin. inhaled formulations comprising insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)NH.sub.2 ; sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; .alpha.2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, insulinotropin, exendin-4, BTS-67582, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone; PPAR-gamma agonists; RXR agonists: JTT-501, MCC-555, MX-6054, DRF2593, GI-262570, KRP-297, LG100268; fatty acid oxidaton inhibitors: clomoxir, etomoxir; .alpha.-glurosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; .beta.-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, both cAMP and cGMP type: sildenafil, L686398: L-386,398; lipid-lowering agents: benfluorex, atorvastatin; antiobesity agents: fenfluramine, orlistat, sibutramine; vanadate and vanadium complexes (e.g., Naglivan.RTM.) and peroxovanadium complexes; amylin antagonists: pramlintide, AC-137; lipoxygenase inhibitors: masoprocal; somatostatin analogs: BM-23014, seglitide, octreotide; glucagon antagonists: BAY 276-9955; insulin signaling agonists, insulin mimetics, PTP1B inhibitors: L-783281, TER17411, TER17529; gluconeogenesis inhibitors:GP3034; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994; glucose transport stimulating agents: BM-130795; glucose synthase kinase inhibitors: lithium chloride, CT98014, CT98023; galanin receptor agonisnts; MTP inhibitors such as those disclosed in U.S. provisional patent application No. 60/164,803; growth hormone secretagogues such as those disclosed in PCT publication numbers WO 97/24369 and WO 98/58947; NPY antagonists: PD-160170, BW-383, BW1229, CGP-71683A, NGD 95-1, L-152804; Anorectic agents including 5-HT and 5-HT2C receptor antagonists and/or mimetics: dexfenfluramine, Prozac.RTM., Zoloft.RTM.; CCK receptor agonists: SR-27897B; galanin receptor antagonists; MCR-4 antagonists: HP-228; leptin or mimetics:leptin; 11-beta-hydroxysteroid dehydrogenase type-I inhibitors; urocortin mimetics, CRF antagonists, and CRF binding proteins: RU486, urocortin. Other anti-diabetic agents that can be used in combination with a glycogen phosphorylase inhibitor include ergoset and D-chiroinositol. Any combination of agents can be

administered as described above.

Brief Summary Text (360):
The compounds of the present invention can also be used in combination with sorbitol dehydrogenase inhibitors. Sorbitol dehydrogenase inhibitors lower fructose levels and have been used to treat or prevent diabetic complications such as neuropathy, retinopathy, nephropathy, cardiomyopathy, microangiopathy, and macroangiopathy. U.S. Pat. Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitof dehydrogenase.

CLAIMS:

13. The pharmaceutical composition of claim 12 wherein the second compound is useful to treat diabetes and is selected from:

insulin and insulin analogs;

GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)--NH.sub.2 ;

sulfonylureas and analogs;

biguanides;

.alpha.2-antagonists;

imidazolines;

glitazones (thiazolidinediones);

PPAR-gamma agonists

fatty acid oxidation inhibitors;

.alpha.-glucosidase inhibitors;

.beta.-agonists;

phosphodiesterase Inhibitors;

lipid-lowering agents:

antiobesity agents

vanadate, vanadium complexes and peroxovanadium complexes;

amylin antagonists;

glucagon antagonists;

gluconeogenesis inhibitors;

somatostatin analogs and antagonists; or

antilipolytic agents.

14. The pharmaceutical composition of claim 12 wherein the second compound is useful to treat diabetes and is selected from:

LysPro insulin, GLP-1 (7-37) (insulinotropin), GLP-1 (7-36)--NH.sub.2, chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; mefformin, phenformin, buformin, midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan, linogliride, ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone, clomoxir, etomoxir, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945, BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, L-386,398; benfluorex, fenfluramine,

(bis(cysteinamide N-octyl)oxovanadium), acipimox, WAG 994, Symlin.TM., (pramlintide acetate) AC2993 or nateglinide.

L4: Entry 13 of 17 File: USPT Aug 27, 2002

DOCUMENT-IDENTIFIER: US 6441015 B2
TITLE: Tetrazole compounds as thyroid receptor ligands

Brief Summary Text (97):
Representative agents that can be used to treat diabetes in combination with a compound of the present invention include insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)--NH.sub.2 ; sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; .alpha.2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, BRL49653; fatty acid oxidation inhibitors: clomoxir, etomoxir; .alpha.-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; .beta.-agonists: BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex; antiobesity agents: fenfluramine; vanadate and vanadium complexes (e.g. Naglivan.RTM.) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994. Also contemplated to be used in combination with a compound of the present invention are pramlintide (symlin.TM.), AC 2993 and nateglinide. Any agent or combination of agents can be administered as described above.

Brief Summary Text (115):
The compounds of the present invention can also be used in combination with a sorbitol dehydrogenase inhibitor. Sorbitol dehydrogenase inhibitors lower fructose levels and have been used to treat or prevent diabetic complications such as neuropathy, retinopathy, nephropathy, cardiomyopathy, microangiopathy, and macroangiopathy. U.S. Pat. Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

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NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded

NEWS EXPRESS	October 14 CURRENT WINDOWS VERSION IS V6.01, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
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FILE 'HOME' ENTERED AT 12:29:20 ON 22 OCT 2002

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FILE 'MEDLINE' ENTERED AT 12:29:37 ON 22 OCT 2002

=> s cardiomyopath?
L1         57011 CARDIOMYOPATH?

=> s (GLP-1) or (glucagon-like peptide-1)
L2          4598 (GLP-1) OR (GLUCAGON-LIKE PEPTIDE-1)

=> s l1 (p) l2
L3             1 L1 (P) L2

=> d ab,bib

L3   ANSWER 1 OF 1  CA  COPYRIGHT 2002 ACS
AB   Hibernating myocardium is characterized by viable myocardium with impaired
     function due to localized reduced perfusion.  Hibernating myocytes retain
     cellular integrity, but cannot sustain high-energy requirements of
     contraction.  High plasma levels of catecholamines, such as
     norepinephrine, are believed to be predictive of mortality from
     hibernating myocardium.  Likewise, high levels of catecholamines lead to
     cardiomyopathy in patients with diabetes.  GLP-1
     reduces plasma norepinephrine levels, and it thus is useful in a method of
     treating hibernating myocardium or diabetic cardiomyopathy.
AN   136:350560  CA
TI   Treatment of hibernating myocardium and diabetic cardiomyopathy
     with a GLP-1 peptide
IN   Ehlers, Mario
PA   Coolidge, Thomas R., USA
SO   PCT Int. Appl., 26 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
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             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
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     US 2002146405     A1   20021010       US 2001-982978   20011022
PRAI US 2000-241834P   P    20001020
     US 2000-242139P   P    20001023
     US 2000-245234P   P    20001103
     WO 2001-US32559   W    20011022


=> s l1 and l2
L4            1 L1 AND L2

=> d ab,bib

L4   ANSWER 1 OF 1  CA  COPYRIGHT 2002 ACS
AB   Hibernating myocardium is characterized by viable myocardium with impaired
     function due to localized reduced perfusion.  Hibernating myocytes retain
     cellular integrity, but cannot sustain high-energy requirements of
     contraction.  High plasma levels of catecholamines, such as
     norepinephrine, are believed to be predictive of mortality from
     hibernating myocardium.  Likewise, high levels of catecholamines lead to
     cardiomyopathy in patients with diabetes.  GLP-1
     reduces plasma norepinephrine levels, and it thus is useful in a method of
     treating hibernating myocardium or diabetic cardiomyopathy.
AN   136:350560  CA
TI   Treatment of hibernating myocardium and diabetic cardiomyopathy
     with a GLP-1 peptide
IN   Ehlers, Mario
PA   Coolidge, Thomas R., USA
SO   PCT Int. Appl., 26 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2002034285     A2    20020502       WO 2001-US32559  20011022
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             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
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     US 2002146405     A1   20021010       US 2001-982978   20011022
PRAI US 2000-241834P   P    20001020
     US 2000-242139P   P    20001023
     US 2000-245234P   P    20001103
     WO 2001-US32559   W    20011022


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     (FILE 'HOME' ENTERED AT 12:29:20 ON 22 OCT 2002)

     FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 12:29:37 ON 22 OCT 2002
L1         57011 S CARDIOMYOPATH?
L2          4598 S (GLP-1) OR (GLUCAGON-LIKE PEPTIDE-1)
L3             1 S L1 (P) L2
L4             1 S L1 AND L2
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End of Result Set

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L9: Entry 2 of 2 File: USPT Dec 11, 2001

DOCUMENT-IDENTIFIER: US 6329389 B1
TITLE: Amine compounds, their production and use

Brief Summary Text (561):
The "hormones" include, for example, growth hormone (GH), growth hormone-releasing hormones (GHRH), thyroid stimulating hormone(TSH), prolactin, insulin, glucagon, etc. The "growth factors" include, for example, insulin-like growth factor-i (IGF-1) and vascular endothelial cell growth factor (VEGF). The "physiologically active substances" include, for example, vasoactive intestinal polypeptide (VIP), gastrin, glucagon-like peptide-1, amylin, substance-P, CCK(cholecystokinin), amylase, interleukins such as interleukin-1 (IL-1) and etc., cytokines such as TNF-.alpha. and etc., cardiotropin, etc.

Brief Summary Text (563):
Compounds (I) and (I') are useful (1) for drugs for treatment of tumors such as acromegaly, TSH-producing tumors, nonsecretory (afunctional) hypophysial tumors, ectopic ACTH (adrenocorticotrophic hormone)-producing tumors, medullar thyroid carcinoma, VIP-producing tumors, glucagon-producing tumors, gastrin-producing tumors, insulinoma and carotinoid tumor, (2) for drugs for treatment of insulin-dependent and non-insulin dependent diabetes mellitus or a variety of diseases associated with them, namely diabetic complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension, (3) for drugs for improvement of hyperinsulinemia or for treatment of obesity caused by inhibition of appetite, and overeating, (4) for drugs for treatment of acute pancreatitis, chronic pancreatitis, pancreal/intestinal fistula, hemorrhagic ulcer, peptic ulcer, gastritis, hyperchylia, regurgitant esophagitis, (5) for drugs for improvement of various symptoms associated with the Helicobacter pylori infection, for example, inhibitors of gastrin hypersecretion, (6) for drugs for inhibition of amylase secretion associated with endoscopic cholangiopancreatography, and drugs for prognostic treatment of surgical operation of pancreas, (7) for drugs for treatment of diarrhea due to intestinal malabsorption, promotion of secretion or dyskinesia of the digestive tracts (for example, short bowel syndrome), diarrhea due to the drugs for cancer chemotherapy, diarrhea due to congenital small intestine atrophy, diarrhea due to neuroendocrine tumors such as VIP-producing tumors, diarrhea due to AIDS, diarrhea due to graft versus host reaction associated with bone marrow transplantation, diarrhea due to diabetes mellitus, diarrhea due to celiac plexus blocking, diarrhea due to systemic sclerosis and diarrhea due to eosinophilia, (8) for drugs for treatment of dumping syndrome, irritable colitis, Crohn disease and inflammatory bowel disease, (9) for drugs for treatment of tumors or cancers (e.g., thyroid cancer, large bowel cancer, breast cancer, prostatic cancer, small cell lung cancer, non-small cell cancer, pancreatic cancer, stomach cancer, cholangiocarcinoma, hepatic cancer, vesical cancer, ovarian cancer, melanoma, osteosarcoma, chondrosarcoma, malignant pheochromocytoma, neuro-blastoma, brain tumors, thymoma, renal cancers), leukemia (e.g., leukemia of basophilic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin disease, and non-Hodgkin lymphoma) (drugs for treatment of these cancers can be used for monotherapy or concomitant therapy with other anticancer drugs such as Tamoxifen, LHRH agonists, LHRH antagonists, interferon-.alpha., .beta. and .gamma., interleukin-2 and etc,), (10) for drugs for prevention and treatment of hypertrophic cardiomyopathy, arteriosclerosis, valvular disease, myocardiac infarction (especially, myocardiac infarction post percutaneous transluminal coronary arterioplasty) and reangioplasty, (11) for drugs for treatment of hemorrhage of

esophageal varicosis, cirrhosis and peripheral blood vessel disorders, (12) for drugs for treatment of diseases associated with general or local inflammation, for example, polyarteritis, rheumatoid arthritis, psoriasis, sunburn, eczema and allergy (e.g., asthma, atopic dermatitis and allergic rhinitis) because they inhibit or modulate the secretion of physiologically active substances acting on the immune system (e.g., Substance P, tachykinin and cytokines), (13) for drugs for treatment of dementia (e.g., Alzheimer disease, Alzheimer-type senile dementia, vascular/multi-infarct dementia), schizophrenia, epilepsy, depression, generalized anxiety disorder, sleep disorder, and multiple sclerosis, because they give influence on the production and secretion of nerve regulators, (14) for drugs for treatment of oculopathy (e.g., glaucoma, etc.), (15) for drugs for prevention and treatment of acute bacterial meningitis, acute virus encephalitis, adult respiratory distress syndrome, bacterial pneumonia, severe systemic mycotic infection, tuberculosis, spinal damage, bone fracture, hepatic failure, pneumonia, alcoholic hepatitis, virus A hepatitis, virus B hepatitis, virus C hepatitis, AIDS infection, human papilloma virus infection, influenza infection, metastasis of cancer, multiple myeloma, osteomalacia, osteoporosis, bone Paget disease, nephritis, renal failure, sepsis, septic shock, hypercalcemia, C: hypercholesterolemia, hypertriglyceridemia, hyperlipemia, systemic lupus erythematosus, transient ischemic attach and alcoholic hepatitis, (16) for cure of organ transplantation, burns, trauma, and alopecia, (17) as analgesics for chronic or acute pain (e.g., postoperative pain, inflammatory pain, dental pain, bone disease (e.g., arthritis, rheumatism, osteoporosis etc.) derived pain), (18) for imaging of tumors having somatostatin receptors after administering radioactive substance (e.g., .sup.123 I, .sup.125 I, .sup.111 In, etc.) to compound (I) or (I') either directly or via a suitable spacer, and (19) for targeting tumors with somatostatin receptors using compound (I) or (I') conjugated with anti-cancer drugs directly or using a suitable spacer.

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L7: Entry 1 of 1 File: USPT Mar 5, 2002

DOCUMENT-IDENTIFIER: US 6352982 B1
TITLE: 4,1-benzoxazepines, their analogues, and their use as somatostatin agonists

Brief Summary Text (300):
The compounds (I) of the present invention or salts thereof may be used in a wide variety of prophylactic, diagnostic, and therapeutic treatments of mammals(for example, human, cattle, horse, dog, cat, monkey, mouse and rat, especially, human) with low toxicity and with less adverse reactions. The compounds (I) of the present invention or salts thereof inhibit or modulate production or secretion of a variety of hormones, growth factors and physiologically active substances of mammals. As said "hormones" are mentioned, for example, growth hormones (GH), thyroid stimulating hormones (TSH), prolactin, insulin and glucagon. As said "growth factors" are mentioned, for example, IGF-1. As said "physiologically active substances" are mentioned, for example, vasoactive intestinal polypeptide (VIP), gastcin, glucagon-like peptide-1, amylin, substance-P, CGRP, CCK(cholecystokinin) and amylase. And that said "physiologically active substance" includes cytokines such as interleukins and TNF-.alpha.. The compounds or salts thereof of this invention function through somatostatin receptors which couple to a variety of intracellular signal transduction systems. These systems include adenylyl cyclase, K.sup.+ channels, Ca.sup.2+ channels, protein phosphatases, phospholipaseC/IP3(inositol 1,4,5-trisphosphate), MAP kinase, a Na.sup.+ /H.sup.+ exchanger, phospholipase A2, a transcription factor such as NF-.kappa.B. The compounds or salts thereof of this invention modulate directly or indirectly cell proliferation inhibitory action of somatostatin and modulate apoptosis induced or regulated by somatostatin. The compounds or salts thereof of this invention may be used in a variety of diseases associated with disorders of production or secretion of hormones, growth factors, and physiologically active substances, associated with disorders of intracellular signal transduction systems, or associated with disorders of regulating cell proliferation. Preferably, the compounds or salts thereof of this invention may be useful (1) for drugs for treatment of for example, tumors such as acromegaly, TSH-producing tumors, nonsecretory (afunctional) hypophysial tumors, ectopic ACTH (adrenocorticotrophic hormone)-producing tumors, medullar thyroid carcinoma, VIP-producing tumors, glucagon-producing tumors, gastrin-producing tumors, insulinoma and cartinoid tumor, (2) for drugs for treatment of insulin-dependent and non-insulin dependent diabetes mellitus or a variety of diseases associated with them, for example, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension, (3) for drugs for improvement of hyperinsulinemia or for treatment of obesity, for example, by inhibition of appetite (4) for drug for treatment of, for example, acute pancreatitis, chronic pancreatitis, pancreatointestinal fisutula, hemorrhagic ulcer, peptic ulcer, gastritis and hyperchylia by inhibition or modulation of the exocrine secretion in the digestive tracts, (5) for drugs for improvement of various symptoms associated with the Helicobacter pylori infection, for example, inhibitors of gastrin hypersecretion, (6) for drugs for inhibition of amylase secretion associated with endoscopic cholangiopancreatography, and drugs for prognostic treatment of surgical operation of pancreas, (7) for drugs for treatment of, for example, diarrhea due to intestinal malabsorption, promotion of secretion or dyskinesia of the digestive tracts(for example, short bowel syndrome), diarrhea due to the drugs for cancer chemotherapy, diarrhea due to AIDS, diarrhea due to graft versus host reaction (GVHR) associated with bone marrow transplantation, diarrhea due to diabetes mellitus, diarrhea due to celiac plexus blocking, diarrhea due to systemic sclerosis and diarrhea due to eosinophilia, (8) for drugs for treatment of, for

example, dumping syndrome, irritable bowel syndrome, Crohn disease and inflammatory bowel disease, (9) for drugs for treatment of, for example, various cancers and tumors of which growth is dependent on insulin or IGF-1 or the other growth factors and various tumors and cancers associated with disorders of regulating cell proliferation caused by the other reasons (for example, thyroid cancer, colorectal cancer, breast cancer, prostatic cancer, small cell lung cancer, non-small cell cancer, pancreatic cancer, stomach cancer, cholangiocarcinoma, hepatic cancer, vesical cancer, ovarian cancer, melanoma, osteosarcoma, chondrosarcoma, malignant pheochromocytoma, neuro-blastoma, brain tumors, thymoma, renal cancers), leukemia (for example, leukemia of basophilic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin disease, and non-Hodgkin lymphoma) (drugs for treatment of these cancers can be used for monotherapy or concomitant therapy with other anticancer drugs, for example, tamoxifen, LHRH agonists, LHRH antagonists, interferon-.alpha., Interferon-.beta., interferon-.gamma. and interleukin-2), (10) for drugs for prevention and treatment of, for example, hypertrophic cardiomyopathy, arteriosclerosis, valvulopathy, myocardiac infarction (especially, myocardiac infarction post percutaneous transluminal coronary arterioplasty) and reangioplasty, (11) for drugs for treatment of hemorrhage of esophageal varicosis, cirrhosis and peripheral blood vessel disorders, (12) for drugs for treatment of, for example, diseases associated with general or local inflammation, for example, polyarteritis, rheumatoid arthritis, psoriasis, sunburn, eczema and allergy (for example, asthma, atopic dermatitis and allergic rhinitis) because they inhibit or modulate the secretion of physiologically active substances acting on the immune system (for example, Substance P, tachykinin and cytokines), (13) for drugs for treatment of, for example, dementia (for example, Alzheimer disease, Alzheimer-type senile dementia, vascular/multi-infarct dementia), headache, migraine, schizophrenia, epilepsy, depression, generalized anxiety disorder, sleep disorder, and multiple sclerosis, because they give influence on the production and secretion of nerve regulators, (14) for analgesic drugs, (15) for drugs for treatment of, for example, acute bacterial meningitis, acute virus encephalitis, adult respiratory distress syndrome (ARDS), bacterial pneumonia, severe systemic mycotic infection, tuberculosis, spinal damage, bone fracture, hepatic failure, pneumonia, alcoholic hepatitis, virus A hepatitis, virus B hepatitis, virus C hepatitis, AIDS infection, human papilloma virus infection, influenza infection, metastasis of cancer, multiple myeloma, osteomalacia, osteoporosis, bone Paget disease, reflux esophagitis, nephritis, renal failure, sepsis, septic shock, hypercalcemia, hypercholesterolemia, hypertriglyceridemia, hyperlipemia, systemic lupus erythematosus, transient ischemic attach and alcoholic hepatitis, (16) for cure of, for example, organ trasplant, burns, trauma, and alopecia, (17) ocular diseases for example glaucoma, (18) for imaging of tumors having somatostain receptor after introducing a radioactive substance (for example, .sup.123 I, .sup.125 I, .sup.111 In) to the compounds of the present invention either directly or via a proper spacer, and (19) targeting tumors with somatostatin receptors using the compounds in the present invention conjugated with anti-cancer drugs directly or using an appropriate spacer.

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NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded

NEWS EXPRESS	October 14 CURRENT WINDOWS VERSION IS V6.01, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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NEWS WWW	CAS World Wide Web Site (general information)

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=> file ca, biosis, medline
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FILE 'BIOSIS' ENTERED AT 12:29:37 ON 22 OCT 2002
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FILE 'MEDLINE' ENTERED AT 12:29:37 ON 22 OCT 2002

=> s cardiomyopath?
L1 57011 CARDIOMYOPATH?

=> s (GLP-1) or (glucagon-like peptide-1)
L2 4598 (GLP-1) OR (GLUCAGON-LIKE PEPTIDE-1)

=> s l1 (p) l2
L3 1 L1 (P) L2

=> d ab,bib

L3 ANSWER 1 OF 1 CA COPYRIGHT 2002 ACS
AB Hibernating myocardium is characterized by viable myocardium with impaired function due to localized reduced perfusion. Hibernating myocytes retain cellular integrity, but cannot sustain high-energy requirements of contraction. High plasma levels of catecholamines, such as norepinephrine, are believed to be predictive of mortality from hibernating myocardium. Likewise, high levels of catecholamines lead to **cardiomyopathy** in patients with diabetes. **GLP-1** reduces plasma norepinephrine levels, and it thus is useful in a method of treating hibernating myocardium or diabetic **cardiomyopathy**.
AN 136:350560 CA
TI Treatment of hibernating myocardium and diabetic **cardiomyopathy** with a **GLP-1** peptide
IN Ehlers, Mario
PA Coolidge, Thomas R., USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002034285	A2	20020502	WO 2001-US32559	20011022

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     US 2002146405     A1   20021010       US 2001-982978   20011022
PRAI US 2000-241834P   P    20001020
     US 2000-242139P   P    20001023
     US 2000-245234P   P    20001103
     WO 2001-US32559   W    20011022


=> s l1 and l2
L4            1 L1 AND L2

=> d ab,bib

L4   ANSWER 1 OF 1  CA  COPYRIGHT 2002 ACS
AB   Hibernating myocardium is characterized by viable myocardium with impaired
     function due to localized reduced perfusion.  Hibernating myocytes retain
     cellular integrity, but cannot sustain high-energy requirements of
     contraction.  High plasma levels of catecholamines, such as
     norepinephrine, are believed to be predictive of mortality from
     hibernating myocardium.  Likewise, high levels of catecholamines lead to
     cardiomyopathy in patients with diabetes.  GLP-1
     reduces plasma norepinephrine levels, and it thus is useful in a method of
     treating hibernating myocardium or diabetic cardiomyopathy.
AN   136:350560  CA
TI   Treatment of hibernating myocardium and diabetic cardiomyopathy
     with a GLP-1 peptide
IN   Ehlers, Mario
PA   Coolidge, Thomas R., USA
SO   PCT Int. Appl., 26 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
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PI   WO 2002034285      A2   20020502       WO 2001-US32559  20011022
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     AU 2002014618     A5   20020506       AU 2002-14618    20011022
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     US 2000-245234P   P    20001103
     WO 2001-US32559   W    20011022


=> d his

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     FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 12:29:37 ON 22 OCT 2002
L1         57011 S CARDIOMYOPATH?
L2          4598 S (GLP-1) OR (GLUCAGON-LIKE PEPTIDE-1)
L3             1 S L1 (P) L2
L4             1 S L1 AND L2
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=> s COX-2 inhibitor?
L5        3680 COX-2 INHIBITOR?

=> s silica/
'SILICA/' IS NOT A VALID FIELD CODE
'SILICA/' IS NOT A VALID FIELD CODE
'SILICA/' IS NOT A VALID FIELD CODE
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=> s silica?
L6      572641 SILICA?

=> s triacetin?
L7        2879 TRIACETIN?

=> s polyethylene glycol?
L8      108169 POLYETHYLENE GLYCOL?

=> s l8 and l7 and l6 and l5
L9            1 L8 AND L7 AND L6 AND L5

=> d ab,bib

L9   ANSWER 1 OF 1  CA  COPYRIGHT 2002 ACS
AB   A pharmaceutical or veterinary paste formulation comprises a drug, fumed
     silica, a viscosity modifier, a hydrophilic carrier, optionally,
     an absorbent and a dye, stabilizer, surfactant, or preservative.  This
     invention also provides for methods of using these formulations for
     treating various disease states as well.  Thus, a paste was prepared containing
     3-(cyclopropylmethoxy)-5,5-dimethyl-4-((4-methylsulfonyl)phenyl)-5H-furan-
     2-one (COX-2 inhibitor) 0.82, TiO2 0.2,
     MgCO3 2, fumed silica 4.25, and PEG-300 0.4% and
     triacetin qs.
AN   135:200445  CA
TI   Pharmaceutical or veterinary paste formulations containing silica
     and viscosity modifier
IN   Jun, Chen
PA   Merial Limited, UK
SO   PCT Int. Appl., 64 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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PI   WO 2001060409      A1   20010823       WO 2001-EP1155   20010205
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             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 2000-504741    A    20000216
RE.CNT  7     THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
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     FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 12:29:37 ON 22 OCT 2002
L1         57011 S CARDIOMYOPATH?
L2          4598 S (GLP-1) OR (GLUCAGON-LIKE PEPTIDE-1)
L3             1 S L1 (P) L2
L4             1 S L1 AND L2
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=> s l1 and l2
L4              1 L1 AND L2
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L1        57011 CARDIOMYOPATH?

=> s (GLP-1) or (glucagon-like peptide-1)
L2         4598 (GLP-1) OR (GLUCAGON-LIKE PEPTIDE-1)

=> s l1 (p) l2
L3            1 L1 (P) L2
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Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Term: L8 not l4

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DATE: Tuesday, October 22, 2002 Printable Copy Create Case

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L9	L8 not l4	2	L9
L8	l6 and l1	10	L8
L7	l6 same l1	1	L7
L6	glucagon-like peptide-1	232	L6
L5	glucagon like-1 peptide	0	L5
L4	l1 and l2	17	L4
L3	l1 same l2	1	L3
L2	GLP-1	489	L2
L1	cardiomyopath$6	2716	L1

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     FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 12:29:37 ON 22 OCT 2002
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